

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY


(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 01 JUN 2006

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Applicant's or agent's file reference PN0411-PCT	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/NO2005/000078	International filing date (day/month/year) 03.03.2005	Priority date (day/month/year) 04.03.2004	
International Patent Classification (IPC) or national classification and IPC INV. A61K51/04 A61K49/00 A61K47/48			
Applicant AMERSHAM HEALTH AS et al.			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 11 sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau a total of 4 sheets, as follows: <input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). <input checked="" type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).			
4. This report contains indications relating to the following items: <input checked="" type="checkbox"/> Box No. I Basis of the report <input type="checkbox"/> Box No. II Priority <input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability <input type="checkbox"/> Box No. IV Lack of unity of invention <input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement <input type="checkbox"/> Box No. VI Certain documents cited <input type="checkbox"/> Box No. VII Certain defects in the international application <input type="checkbox"/> Box No. VIII Certain observations on the international application			
Date of submission of the demand 05.12.2005		Date of completion of this report 31.05.2006	
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016		Authorized officer González Ramon, N. Telephone No. +31 70 340-3466	



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/NO2005/000078

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-32 as originally filed

Claims, Numbers

1-11 received on 06.02.2006 with letter of 06.02.2006

Drawings, Sheets

1/1 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☒ the claims, Nos. 9
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 1-11 in part

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*).
- ☒ no international search report has been established for the said claims Nos. 1-11 in part
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☒ See separate sheet for further details

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	2,5
	No: Claims	1, 3, 4, 6-8, 10,11
Inventive step (IS)	Yes: Claims	
	No: Claims	1-8, 10, 11
Industrial applicability (IA)	Yes: Claims	1-8, 10, 11
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item I

Basis of the report

The present opinion has been not been established for the amended claim 9 that extends beyond the content of the application as filed.

Said amended claim reading "Z denotes a chelating agent of formula (VII) that optionally can carry an imaging moiety, **and one or more biomodifiers groups selected from...**"

Said biomodifiers are disclosed in the application as filed only in connection to the V or L groups of formula I (page 15 second paragraph), whereas such biomodifiers are not originally disclosed connected to the Z group and therefore the present claim 9 extends beyond the content of the application as filed.

This international preliminary examination report has been established as if said amendment had not been made (Rule 70.2© PCT)

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

In the present application, the International Searching Authority has restricted the search under the following objections under Articles 5 and 6 PCT:

Present claims 1-8, 10, 11 relate to compounds defined by reference to vague characteristics or properties, namely "2 or more R groups, together with the atoms to which they are attached for a carbocyclic, heterocyclic, saturated or unsaturated ring" (claim 5); "a peptide chelate conjugate" (claim 11). In fact, the claims contain so many options,

variables and possible permutations that a lack of clarity within the meaning of Article 6 PCT arises.

The claims cover all compounds having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds.

Moreover claims 1-8, 10, 11 encompass a genus of compounds defined only by their function, namely "a linker", "an imaging moiety", "an ACE cleavage site", "imageable moiety capable of detection either directly or indirectly in a diagnostic imaging procedure" (claim 1); "a biomodifier group" (claim 3); "a chelating agent" (claim 4); "a moiety which emit or cause to emit detectable radiation", "a moiety which affect local electromagnetic fields"; "moieties which absorb or scatter radiation energy", "moieties which generate a detectable substance" (claim 6); "a reducing agent" (claim 10), wherein the relationship between the structural features of the members of the genus and said function have not been defined.

In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition.

The fact that one could have assayed a compound of interest using the described assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed.

It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.

Therefore, the claims do not fulfil the requirements of Art. 5 and Art. 6 PCT.

Support is only to be found in the present application for those parts relating to the compounds effectively disclosed in the examples and those specifically mentioned by chemical name in claims 2, 7, 8 in connection with linkers as recited in description page

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(SEPARATE SHEET)**

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10, lines 4-10 and biomodifiers as in page 15, lines 2-14, and as such has been the subject of the search.

No opinion will be formulated in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT)

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

The following documents (D) are referred to in this communication:

- D1: WO 93/12819 A (RHOMED INCORPORATED) 8 July 1993.
- D2: WO 98/18496 A (NYCOMED IMAGING AS; COCKBAIN, JULIAN; KLAIVENESS, JO; NAEVESTAD, ANNE;) 7 May 1998.
- D3: WO 02/20610 A (MALLINCKRODT INC; SCHMIDT, MICHELLE, A; ERION, JACK, L; SRINIVASAN, AN) 14 March 2002.
- D4: US-A-3 966 896 (GLOVSKY ET AL) 29 June 1976.
- D5: CHAUVEAU D. ET AL: BR J. CLIN PHARMAC, vol. 33, 1992, pages 253-260, XP008054562.
- D6: GLOSSMANN H. ET AL: JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 249, 1974, pages 825-834, XP008054573.
- D7: LIU S ET AL: CHEMICAL REVIEWS, ACS, WASHINGTON, DC, US, vol. 99, no. 9, September 1999 (1999-09), pages 2235-2268, XP000852433.
- D8: WO 03/006491 A (AMERSHAM HEALTH AS) 23 January 2003.
- D9: BAKER K. M. ET AL: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL

THERAPEUTICS, vol. 239, no. 3, 1986, pages 790-796, XP008054564
D10: BORGHHERESI R. A. M. B. ET AL: COMP BIOCHEM PHYSIOL, vol. 113B,
no. 3, 1996, pages 467-473, XP008054747.

Novelty (Art 33 (2) PCT)

The subject-matter of claims 1, 3, 4, 6-8, 10, 11 is not new in the sense of Article 33(2) PCT. The reasons therefore are the following:

D1 discloses peptide-metal ion pharmaceutical compositions including labelled angiotensin I, a decapeptide of sequence embraced by present claim 1 (see claims 1, 5, 10; example 24). The metal binding domain consist on a part of the peptide sequence and the metal ions used include ⁹⁹Tc and isotopes of Mo and Tl (see page 16, lines 25-35). A reducing agent is used in their preparation (see page 25, lines 16-40). Consequently the subject matter of claims 1, 4, 6-8, 10, 11 is not new over D1.

D3 discloses labelled peptides including angiotensin which is as such embraced under claim 1 of the present application (see claims 5, 10, 15) and a chelating moiety or a metal binding site for imaging and therapy. Labelling metal isotopes include ⁹⁹Tc, ⁶⁷Ga and ¹¹¹In (see claims 2, 7, 12, 23). Consequently the subject matter of present claims 1, 4, 6, 7, 10 is not new over D3.

D4 discloses ¹²⁵I Radioactive labelled angiotensin I, decapeptide embraced by present claim 1 (see abstract; claims 12, 23). Therefore rendering the subject matter of present claims 1, 6, 7 not novel.

D5 discloses ¹²⁵I labelled angiotensin I, decapeptide embraced by present claim 1 (see page 255, col. 1, paragraph 2). Consequently the subject matter of present claims 1, 6, 7 is not new over D5.

D6 discloses ¹²⁵I angiotensin I, decapeptide embraced by present claim 1 and its uptake in the bovine and rat adrenal cortex (see abstract; figure 9). Therefore rendering the subject matter of present claims 1, 6, 7, 10 not novel.

Inventive step (Art 33(3) PCT)

Should the applicant overcome the above raised objections, an inventive step has to be demonstrated for the subject matter of present claims 1-8, 10, 11 (Art 33(3) PCT).

According to the description (page 6, paragraph 3), the problem underlying the present invention is the non-specific and low binding affinity to the Angiotensin type I receptor AT1 receptor of the native octapeptide Ang II and related radiolabeled compounds.

As solution to this problem a compound comprising a Angiotensin I homologous family decapeptide with a fixed central sequence Val-Tyr-Ile-His-Pro and variable aminoacid substitutions in positions 1, 2, 8, 9, 10 conjugated to an imaging moiety as depicted in claim 1 is proposed.

Previously discussed document D2, which can be considered the closest prior art, discloses a composition of formula V-L-R wherein V is a group having binding affinity for angiotensin II receptor site including oligopeptides having the motif Arg-Val-Tyr-Ile-His-Pro of present claim 1, L is a linker or a bond and R is a detectable moiety in vivo imaging including ^{131}I , ^{99}Tc , ^{111}In , ^{67}Ga , ^{68}Ga and further derivatised with a PEG chain.

The difference between D2 and the subject matter of present claims is the particular use of decapeptide of sequence as depicted by present claim 1 as well as the use particular aminoxime chelating agent embraced by formula (VII) of present claim 5 are not explicitly disclosed by D2

The sequence modification of small peptides (as presented in present claim 1) cannot be considered as conferring an inventive step to the subject matter of the present application.

The skilled person is prompted from the general knowledge in peptide chemistry to tune aminoacid substitutions in order to achieve a desired specificity for a target, not relying in any inventive skill but purely by a routine laboratory practice in the field of small peptide tailor-made sequence synthesis.

Several documents in the art would reinforce the skill person on such sequence

modification in order to achieve improvement in the peptide sequence (in particular conserving the central sequence Val-Tyr-Ile-His-Pro as claimed by the present application), as i.e. D9, where decapeptide angiotensin I analogs with aminoacid substitutions in positions 1, 5 and 7 exhibit both cardiac (+)-inotropic and vascular contractile activities (see page 794, col. 2- page 795) or D10 presenting angiotensin I peptide sequences in Human, ox, chicken, frog, alligator, turtle and snakes species wherein variations and non conservative amino acids stand in particular in position 1, 5 and 9 of the decapeptide (see figure 6).

In respect to the use particular aminoxime chelating agent embraced by formula (VII) of present claim 5:

D7 describes ^{99m}Tc labelled small peptides as diagnostic radiopharmaceuticals. Amineoxime chelating agents are used as bifunctional chelator. Direct labelling as well as prelabeling and postlabelling approach are described (see table 1; figures 2, 11; page 2245, col. 2; page 2252)

D8 describes RGD Peptide conjugates with amine oxime chelating agents embraced under formula (VII) of present application including the preferred chelating agent pn216 (see page 10, lines 5-10; page 12). Reporters include chelatable metals as ⁹⁹Tc, ¹¹¹In, ⁶⁷Ga and radioactive isotopes as ¹²³I, ¹³¹I, ¹⁸F (see page 22, line 26-page 24, line 34). Pharmaceutical compositions comprising the same and use as diagnosis imaging agents are also described (see claims 12, 22-24)

Both documents D7, D8 describe a wide range of small peptide compounds modified in order to include the amine oxime chelant of formula VII and therefore render obvious such structural modification of a decapeptide as claimed by present claim 5.

Furthermore, the attention of the applicant is also drawn to the fact that all embodiments covered by the claims should satisfy the criteria of inventive step.

When the inventive step is solely based on the achievement of a technical effect, such as the specific and high binding affinity to the Angiotensin type I receptor AT1 receptor, substantially all embodiments of independent claim 1 (i. e. any compound embraced under formula I as depicted) should exhibit this effect.

However, it is evident that the number of compounds comprising groups encompassed under "a linker", "a peptide chelate conjugate"; "an imaging moiety", "an ACE cleavage site", "imageable moiety capable of detection either directly or indirectly in a diagnostic imaging procedure" (claim 1); "a biomodifier group" (claim 3); "chelating agent" (claim 4); "2 or more R groups, together with the atoms to which they are attached for a carbocyclic, heterocyclic, saturated or unsaturated ring" (claim 5); "a moiety which emit or cause to emit detectable radiation", "a moiety which affect local electromagnetic fields"; "moieties which absorb or scatter radiation energy", "moieties which generate a detectable substance" (claim 6); "a reducing agent" (claim 10); is such that it is unlikely that all of them possess the effect claimed.

Moreover taking into account previously discussed documents D9, D10 wherein structural modifications in the sequence are restricted to one/two positions in the molecule since the unpredictable effect of simultaneous change of several aminoacids of a peptide sequence deeply affects the pharmacological action of the peptide.

Therefore, as part of the subject matter of claims 1-8, 10, 11 does not exhibit this particular technical effect in a credible manner, said subject matter cannot involve inventive step.

Consequently an inventive step for the subject matter of claims 1-8, 10, 11 cannot be acknowledged.

Claims

1. A pharmaceuticals characterized by general formula (I)



wherein

V denotes a peptide with a binding sequence $-X^1-X^2-\text{Val-Tyr-Ile-His-Pro-}X^8-X^9-X^{10}$,

L denotes bond or a linker,

Z denotes a group that optionally can carry an imaging moiety M,

X^1 denotes $-\text{NY}_1-(\text{CH}_2)_m-\text{CO}-$ where m is an integer from 1 to 10 and Y_1 is H or an alkyl or aryl containing substituent,

X^2 denotes Arg, N-alkylated Arg, a Arg mimetics Phe[4-guanidino] or Gly-4-piperidyl[N-amidino],

X^8 denotes Gly, Phe, Phg, Hph, Bip, Ala, Tyr, His, Trp or Nal,

X^9 and X^{10} denote, independent of each other, Pro, Arg, His, Ala, Phe, Glu, Leu, Val, Ile, Met, Trp, Asp or Lys and where X^8 , X^9 and X^{10} together constitute an ACE cleavage site

and wherein the residues Val and Ile at position 3 and 5 respectively may optionally be replaced with amino acids capable of forming a bridging unit wherein the bridge containing a $-\text{CH}_2-\text{CH}_2-$, $-\text{S}-\text{CH}_2-$, $-\text{S}-\text{CH}_2-\text{S}-$, lactam or $-\text{S}-\text{S}-$ unit,

Z forms a bond with the amino acid X^1 optionally through the linker L, and

M where present denotes an imageable moiety capable of detection either directly or indirectly in a diagnostic imaging procedure.

2. A pharmaceutical according to claim 1 wherein the amino acid of X^1 , X^2 , X^8 , X^9 , X^{10} are independently selected from

X^1 denoting Gly

X^2 denoting Arg or N-Methyl-Arg

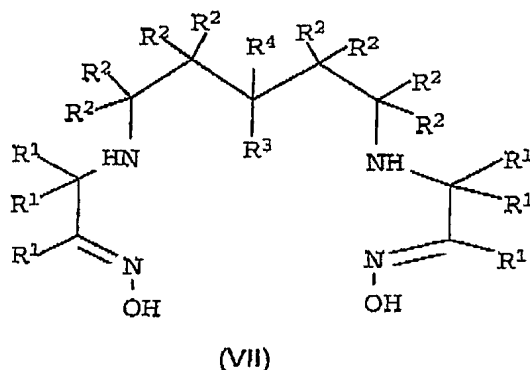
X^8 denoting Phe

X^9 denoting Pro, Arg, His, Ala, Phe, Glu, Leu, Val, Ile, Met, Trp, Asp or Lys and

X^{10} denoting Pro, Arg, His, Ala, Phe, Glu, Leu, Val, Ile, Met, Trp, Asp or Lys.

3. A pharmaceutical according to the preceding claims further comprising one or more biomodifier groups are attached to any positions of the V and L groups of formula (I)

4. A pharmaceutical according to the preceding claims wherein Z denotes a chelating agent.
5. A pharmaceutical according to claim 4 wherein Z denotes the chelating agent of formula (VII)

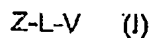


wherein:

each R^1 , R^2 , R^3 and R^4 is independently H or C_{1-10} alkyl, C_{3-10} alkylaryl, C_{2-10} alkoxyalkyl, C_{1-10} hydroxyalkyl, C_{1-10} alkylamine, C_{1-10} fluoroalkyl, or 2 or more R groups, together with the atoms to which they are attached form a carbocyclic, heterocyclic, saturated or unsaturated ring.

6. A pharmaceutical according to any of the preceding claims wherein M represents an imageable moiety for the use in diagnosis particularly in *in vivo* diagnosis comprising a moiety which emit or cause to emit detectable radiation, a moiety which affect local electromagnetic fields, moieties which absorb or scatter radiation energy, heavy metals and compounds thereof and moieties which generate a detectable substance.
7. A pharmaceutical according to claim 6 wherein M represents a gamma emitting moiety for Radio or SPECT imaging comprising ^{67}Ga , ^{111}In , ^{123}I , ^{125}I , ^{131}I , $^{81\text{m}}\text{Kr}$, ^{99}Mo , $^{99\text{m}}\text{Tc}$, ^{201}Tl and ^{133}Xe .
8. A pharmaceutical according to claim 6 wherein M represents a radio emitter with positron emitting properties for PET imaging comprising ^{11}C , ^{18}F , ^{68}Ga , ^{13}N , ^{15}O and ^{82}Rb .

9. A pharmaceuticals according to claims 1 to 5 characterized by general formula (I)



wherein

V denotes a peptide with a binding sequence $-X^1-X^2-\text{Val-Tyr-Ile-His-Pro-}X^8-X^9-X^{10}$, wherein the amino acid of X^1 , X^2 , X^8 , X^9 , X^{10} are independently selected from

X^1 denoting Gly

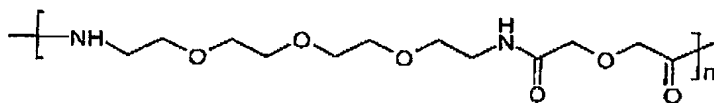
X^2 denoting Arg or N-Methyl-Arg

X^8 denoting Phe

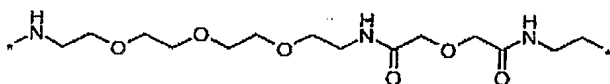
X^9 denoting Pro, Arg, His, Ala, Phe, Glu, Leu, Val, Ile, Met, Trp, Asp or Lys and

X^{10} denoting Pro, Arg, His, Ala, Phe, Glu, Leu, Val, Ile, Met, Trp, Asp or Lys.

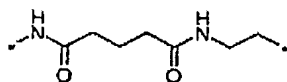
L denotes a bond or a linker selected from compounds of formula $\text{NH}-(\text{CH}_2)_m-$ optionally combined with $-\text{CO}-(\text{CH}_2)_m-\text{CO}-$ where m denotes a positive integer from 1 to 10, one or more units of compounds of formula (IV) wherein n is an integer from 1 to 10, compounds of formula (X) or (VI)



Formula (IV)



Formula (X)



Formula (VI)

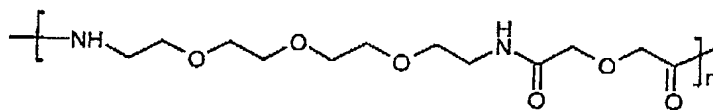
Z denotes a chelating agent of formula (VII) that optionally can carry an imaging moiety M, and one or more biomodifier groups selected from monodisperse PEG building block comprising 1 to 10 units of said building block or the compound of formula IV,

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Formula (IV)

wherein n equals an integer from 1 to 10 are attached to any positions of the V and L groups of formula (I).

10. Pharmaceutical formulation comprising a pharmaceutical of formula (I) of claim 1 together with one or more pharmaceutical acceptable additives and/or excipients.

11. A kit for the preparation of a radiopharmaceutical composition of formula (I) comprising a peptide-chelate conjugate and a reducing agent.